REMARKS

This document is filed in reply to the office action dated July 3, 2003 ("Office Action"). Applicants have amended the specification to correct a typographic error. No new matter has been introduced. Claims 1-20 are pending. Reconsideration of the application, as amended, is requested in view of the following remarks:

Rejection under 35 U.S.C. § 112, second paragraph

The Examiner rejected claims 1, 2, 4, 6, 7, 9, 11, 12, 14, 16, 17, and 19 for indefiniteness, contending that the phrase "threshold level" recited in these claims is not defined. The Examiner acknowledged that the specification, at page 2, paragraph 2, describes a method for determining the threshold level based on the survival curves of groups of patients. Nonetheless, she asserted:

> [T]he specification states that "[t]he threshold levels of expression for exclusion or inclusion in any group is set to achieve **pre-determined levels of survival**." Thus, a **pre-determined survival probability** must be known in order to segregate patients on the basis of maspin expression. As the claims 1-10 are drawn to determining a probability of survival, it appears that the guidance [on "threshold level"] given in the specification is not adequate for the determination of a "threshold level."

The Examiner apparently misinterpreted "pre-determined levels of survival" as "probabilities of survival" and believed that the latter must be known to segregate patients in order to set threshold levels. As claims 1-10 indicate that the threshold levels are needed to determine the probabilities of survival, the Examiner concluded that there is circle in the description of "a threshold level."

Applicants would like to point out that pre-determined levels of survival are established based on the actual survival curves of patients according to the method described at page 2, paragraph 2 of the specification. They differ from probabilities of survival, which are predicted based on maspin expression levels according to the methods of claims 1-10. The former, but not the latter, must be known to determine a threshold level. As the specification clearly describes a method of obtaining the former and determining threshold levels, the claims at issue are definite.

Rejection under 35 U.S.C. § 103(a)

The Examiner rejected all pending claims for obviousness over U.S. Patent 5,470,970 to Sager et al., ("Sager") in view of Ding et al., (Proc. Amer. Assoc. Cancer Res., 1996 Vol. 39, page 90, "Ding"), Rheinwald et al., (Cancer Research, 1981, Vol. 41, pp. 1657-1663, "Rheinwald"), Pemberton et al., (J. Histochemistry & Cytochemistry, 1997, Vol. 45, pp 1697-1706, "Pemberton"), the abstracts of Petrovich et al. (Radiology 144(4): 905-908, 1982), Weber et al. (Otolaryngology – Head and Neck Surgery 99(1): 16-23, 1988), Tytor et al. (Clinical Otolaryngology 15(3): 235-252, 1990), Eiband et al. (American Journal of Surgery 158(4): 314-317, 1989), Huwer et al. (European Journal of Cardio-Thoracic Surgery 6(9): 498-502, 1992), Nagel et al. (Zentralblatt fur Chirurgie 119(4): 225-232, 1994), and van der Velden et al. (Cancer 75(12): 2885-2890, 1995).

Applicants respectfully traverse and will discuss claims 1 and 11 first. Claim 1 is drawn to a method of determining a relative probability of survival for a subject with squamous cell carcinoma. Claim 11 is drawn to a method of determining whether a subject with squamous cell carcinoma has a lymph node containing cancerous cells. Both methods include (1) determining a level of maspin gene expression in a biological sample from a subject with squamous cell carcinoma; and (2) comparing the level with a threshold level of maspin gene expression. If the level of maspin gene expression in the biological sample is above the threshold level, it indicates that the subject has a relatively high probability of survival or is free of a lymph node containing cancerous cells.

It is the Examiner's position that Sager, the primary reference, teaches a method of staging a carcinoma based on a correlation between the level of maspin gene expression and the stage of a carcinoma, in which a lower expression level is indicative of a later stage. It does not teach applying the correlation to stage squamous cell carcinoma. According to the Examiner, Sager teaches that a carcinoma to be staged "is derived from a type of cell which normally expresses the maspin gene..." The Examiner then alleged that the secondary references teach that the Sager method can be used in squamous cell carcinoma. In particular, she pointed out that Ding, Rheinwald, and Pemberton teach that (1) maspin was commonly overexpressed in

squamous cell carcinoma lines, e.g., SCC4; (2) SCC4 is derived from human squamous cell carcinoma of the tongue; and (3) maspin is associated with the squamous epithelium of the tonsil, respectively. The Examiner then concluded that it would have been prima facie obvious to one skilled in the art to apply the correlation taught by Sager to squamous cell carcinoma and that one skilled in the art would have been motivated to do so with a reasonable expectation of success.

Applicants respectfully traverse. The method of Sager is based on the discovery that the level of maspin expression decreases during progression to breast cancer. See, e.g., column 3, lines 2-13. There is no indication in Sager that the level of maspin expression also decreases during progression to squamous cell carcinoma. None of the secondary references mentions the down-regulation of the level of maspin gene expression during squamous cell carcinoma development. On the contrary, Ding teaches that "maspin was commonly overexpressed in squamous cell carcinoma lines," i.e., the level of maspin expression increases during progression to squamous cell carcinoma. In other words, Ding **teaches** one skilled in the art **away** from applying the correlation taught by Sager to squamous cell carcinoma.

As mentioned in the specification, the methods of claims 1 and 11 are based on a positive correlation between the level of maspin gene expression in patients with squamous cell carcinoma and the relative probability of survival for those patients. See page 1, lines 10-12. None of the references cited by the Examiner suggests this positive correlation in patients having squamous cell carcinoma. Indeed, Ding **teaches away** from this correlation. Thus, claims 1 and 11 are non-obvious over the references.

Like claims 1 and 11, claims 6 and 16 also cover methods that are based on the just-mentioned positive correlation. For the same reasons set forth above, claims 6 and 16 are non-obvious. So are claims 2-5, 7-10, 12-15, and 17-20, all of which depend from claims 1, 6, 11, and 16.

CONCLUSION

Applicants submit that grounds for the rejections asserted by the Examiner have been overcome, and that claims, as pending, define subject matter that is definite and non-obvious. On this basis, it is submitted that allowance of this application is proper, and early favorable action is solicited.

Please apply any other charges to deposit account 06-1050.

Respectfully submitted,

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